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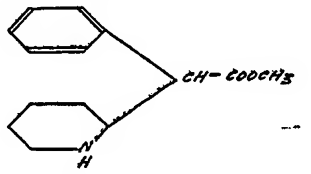
COMPLETE SPECIFICATION

Stereoisomers of α-Phenyl-α-Piperidyl-(2)-Acetic Acid and process of making same

We, CIBA LIMITED, a body corporate organised according to the Laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the conversion of stereoisomers of α-phenyl - α-piperidyl-(2)-acetic acid.

The manufacture of α-phenyl-α-piperidyl-(2)-acetic acids and its functional acid derivatives such as esters and amides and also their functional conversion are known (cf. for example British Patent No. 589,625). The esters, especially the α-phenyl-α-piperidyl-(2)-acetic acid methyl ester of the formula



are distinguished by a stimulating effect.

The present invention is based on the observation that the α-phenyl-α-piperidyl-(2)-acetic acids obtained by synthesis, and also its functional acid derivatives, can be resolved by physical means, especially crystallization, into two racemates. As a result it was discovered that in the case of the ester racemates it is only one of the two racemates which possesses the above specified therapeutic properties, whereas the other is practically inactive. Moreover, it was possible to obtain the two optically active antipodes of the pharmacologically active racemates. One of them has a considerably greater therapeutic effect than the other.

The pharmacologically active ester-racemates and their optically active antipodes, as also the corresponding racemates and antipodes of the acid and other functionally converted carboxyl derivatives, are hereinafter designated by the letter b, b_1 representing the pharmacologically active ester-antipode and b_2 the less active ester-antipode or the corresponding acids or its derivatives; the other racemates are called a-racemates and the corresponding antipodes are called a-antipodes, or more exactly a_1- and a_2-antipodes.

A further feature of the present invention consists in a process for the conversion of the a-racemates or a-antipodes into the racemates or antipodes of the b series which are of value as medicaments or for the manufacture of medicaments. This process consists in that the a-racemates or a-antipodes of α-phenyl-α-piperidyl-(2)-acetic acids or its functional derivatives are treated with alkaline agents, if desired the b-racemate or b-antipode isolated from the product which results and further, if desired, before or after the isolation, the free or functionally converted carboxyl group subjected to conversion.

As starting materials there can be used pure a-racemates, a-antipodes or a racemate mixture of α-phenyl-α-piperidyl - (2) - acetic acids or of its functional acid derivatives such as esters, especially of low alkanols, primarily methanol, or also amides. As alkaline agents there can be used for example alkali metal or alkaline earth hydroxides or alcoholates or strong organic bases, as for example trimethyl-benzyl-ammonium hydroxide, which are preferably used at elevated temperature.

Starting from a-racemates or racemate mixtures, mixtures of a- and b-racemates are obtained. However, if a-antipodes are used, optically active products are obtained instead of the expected racemates, in that from a_1-antipodes b_1-antipodes of opposite rotation are formed and from the a_2-antipodes b_2-antipodes are obtained analogously. This shows that,

[Price 3s 6d] 4s 6d

Price 25p

contrary to expectation the rearrangement in this process takes place at only one of the two asymmetrical carbon atoms. It has been found that the isolation of the pure *b*-racemate or *b*-antipode is best carried out at the stage of the free-α-phenyl-α-piperidyl-(2)-acetic acid by crystallisation from water at a pH value of about 6. The free acid may then be converted into the desired esters by conventional methods.

The *a*-racemates to be used as starting materials can be made, for example, by the process of the aforementioned British Patent No. 589,625. The *a*-antipodes can be obtained from the *a*-racemates by means of optically active tartaric acid by the usual methods.

The racemates and antipodes of the α-phenyl-α-piperidyl-(2)-acetic acids or of its derivatives which are produced as products of the present process, especially the *b*-racemate and the b_1-antipode of α-phenyl-α-piperidyl-(2)-acetic acid methyl ester, can be used as medicaments or as intermediate products therefor. The present invention also extends to pharmaceutical preparations which contain in admixture with a carrier material suitable for therapeutic application, e.g. enteral or parenteral administration, of the stereoisomers of an α-phenyl-α-piperidyl-(2)-acetic acid ester the *b*-racemate only or b_1-antipode. In these preparations the content of *b*-racemate or b_1-antipode per unit dose advantageously amounts to at least 1 mg and at most 50 mg. As carrier materials such substances are concerned as do not react with the new compounds, as for example, water, gelatine, lactose, starch, magnesium stearate, talc, vegetable oils, benzyl alcohols, gum, polyalkylene glycols, petroleum jelly, cholesterol or other known medicament carriers. The pharmaceutical preparations can, for example, be made up as tablets, dragees, salves, creams or in liquid form as solutions, suspensions or emulsions. They may, if desired, be sterilized and/or may contain auxiliary substances, such as preserving, stabilizing, wetting or emulsifying agents or salts which have the effect of varying the osmotic pressure or also buffer substances. They may also contain other substances of therapeutic value. These pharmaceutical preparations are produced by the conventional methods.

The following Examples illustrate the invention, the relation between part by weight and part by volume being the same as that between the gram and the cubic centimeter:

EXAMPLE 1.

50 parts by weight of α-phenyl-α-piperidyl (2)-acetic acid methyl ester hydrochloride, having a content of about 20 per cent. of *b*-racemate and prepared according to Example 1 of British Patent No. 589,625 are dissolved in a little water, the solution covered with a layer of ether and 1.5 equivalents of aqueous 50 per cent caustic potash solution added thereto. After the separation of the ether layer, the aqueous layer is extracted twice with ether and the combined ether solutions then evaporated to dryness. The residue amounts to 43 parts by weight. It is mixed with 50 parts by weight of potassium hydroxide, dissolved in 100 parts by volume of water, and the mixture boiled for 4 hours under reflux. On cooling, the reaction solution separates into two layers. The upper consists of a mixture of the potassium salts of the two stereoisomeric α-phenyl-α-piperidyl-(2)-acetic acid racemates, which mixture becomes solid after a few hours standing at 20° C. It is diluted with 110 parts by volume of water and brought to pH = 6.0 with 137 parts by volume of 2N-sulfuric acid. The *b*-racemate of α-phenyl-α-piperidyl-(2)-acetic acid is precipitated while the *a*-racemate remains in solution. The precipitate is granular and well suited to filtration with suction. After several hours drying at 100° C. it weighs 24.2 parts by weight and consists of pure *b*-racemate of α-phenyl-α-piperidyl-(2)-acetic acid.

Re-esterification to *b*-racemates of α-phenyl-α-piperidyl-(2)-acetic acid esters and the formation of the corresponding hydrochlorides can be carried out by conventional methods.

As an example, the methyl ester hydrochloride is obtained by suspension of 1 part by weight of the *b*-racemates of α-phenyl-α-piperidyl-(2)-acetic acid in 3.5 parts by volume of methanol and by boiling for 2 hours under reflux with passage of dry hydrogen chloride gas. After the cooling of the solution, the *b*-racemate of α-phenyl-α-piperidyl-(2)-acetic acid methyl ester hydrochloride crystallizes in fine prisms of melting point 208—209° C.

The *b*-racemate of the butyl ester hydrochloride is obtained in an analogous manner by stirring for 2 hours one part by weight of *b*-racemate of α-phenyl-α-piperidyl-(2)-acetic acid in 4 parts by volume of *n*-butanol in a stream of hydrogen chloride at 80° C. The *b*-racemate of the α-phenyl-α-piperidyl-(2)-acetic acid butyl ester hydrochloride, which crystallizes on cooling, can be recrystallized from acetone and melts at 165° C.

EXAMPLE 2.

116 parts by weight of the *a*-racemate of α-phenyl-α-piperidyl-(2)-acetic acid hydrochloride are boiled under reflux for 5 hours with 2000 parts by weight of potassium hydroxide dissolved in 2000 parts by volume of water. The whole reaction solution is then neutralized with hydrochloric acid to pH = 6.0 with simultaneous dilution with water to 10,000 parts by volume. A granular precipitate is deposited which consists of a mixture of potassium chloride and the *b*-racemate of α-phenyl-α-piperidyl-(2)-acetic acid. The potassium chloride can be removed by washing with water. In this manner 69 parts by weight of *b*-racemate of α-phenyl-α-piperidyl-

(2)-acetic acid are obtained, which can be esterified by the method described in Example 1. It is also possible, however, to effect the esterification using the mixture of potassium chloride and *b*-racemate.

The *a*-racemate of α-phenyl-α-piperidyl-(2)-acetic acid hydrochloride, which is used as starting material, can be obtained, for example, as follows:

50 parts by weight of α-phenyl-α-piperidyl-(2)-acetic acid methyl ester hydrochloride with a content of about 20 per cent of *b*-racemate are treated with caustic potash solution as described in Example 1. The separated mixture of the potassium salts of the stereoisomeric α-phenyl-α-piperidyl-(2)-acetic acid racemates is diluted with 110 parts by volume of water and brought to pH = 6 with 137 parts by volume of 2N-hydrochloric acid. The precipitated *b*-racemate is filtered with suction and the mother liquor evaporated to dryness. The residue is recrystallized from 6N-hydrochloric acid. In this manner pure *a*-racemate of α-phenyl-α-piperidyl-(2)-acetic acid hydrochloride is obtained.

EXAMPLE 3.

25 parts by weight of crude α-phenyl-α-piperidyl-(2)-acetamide, obtained by catalytic hydrogenation of α-phenyl-α-pyridyl-(2)-acetamide as described in Example 1 of British Patent No. 589,625 with a content of about 30 per cent of *b*-racemate, are boiled for 10 hours under reflux with 25 parts by weight of potassium hydroxide dissolved in 50 parts by volume of water. After cooling, 23.5 parts by weight are deposited of a racemate mixture of α-phenyl-α-piperidyl-(2)-acetamide with an increased content of *b*-racemate, which mixture is filtered with suction, washed with a little cold water and hydrolyzed to α-phenyl-α-piperidyl-(2)-acetic acid by 6 hours' boiling with 47 parts by volume of 40 per cent sulfuric acid. The hydrolysis solution is brought to pH = 6.0 with caustic potash solution with simultaneous dilution with water to 400 parts by volume. 19 parts by weight are deposited of *b*-racemate of α-phenyl-α-piperidyl-(2)-acetic acid, which can be esterified as described in Example 1.

EXAMPLE 4.

500 parts by weight of crude α-phenyl-α-piperidyl-(2)-acetamide with a content of *a*-racemate of 68 per cent, prepared according to Example 1 of British Patent No. 589,625 are dissolved in 2000 parts by volume of absolute ethyl alcohol, the solution saturated with dry hydrogen chloride gas and the whole allowed to stand for 2 hours at 5—10° C. 425 parts by weight of nearly pure *a*-racemate of α-phenyl-α-piperidyl-(2)-acetamide hydrochloride crystallize out. This product is boiled under reflux for 16 hours with 425 parts by weight of potassium hydroxide dissolved in 850 parts by volume of water. The racemate mixture of α-phenyl-α-piperidyl-(2)-acetamide, which precipitates on cooling, together with the evaporation residue from the above obtained alcoholic mother liquor from the *a*-racemate and which consists of practically pure *b*-racemate, is hydrolyzed by boiling for 6 hours with 1300 parts by volume of 40 per cent sulfuric acid. By dilution and neutralization of the hydrolysis solution to pH = 6 a precipitate is obtained of *b*-racemate of α-phenyl-α-piperidyl-(2)-acetic acid which is isolated as described in Example 1. Yield 382 parts by weight.

EXAMPLE 5.

40 parts by weight of the crude α-phenyl-α-piperidyl-(2)-acetamide as used in Example 4 are stirred for 2 hours at 100° C. with 200 parts by volume of a 40 per cent solution of trimethylbenzyl ammonium hydroxide in water. Thereupon, with cooling, the whole is brought to pH = 9.9 with 6N-hydrochloric acid and the solution exhaustively extracted with ethylene chloride. The ethylene chloride residue is hydrolyzed with 40 per cent sulfuric acid in a manner analogous to that described in Example 4 and the hydrolysis solution also worked up in an analogous manner to that described in the said Example. In this manner 19.9 parts by weight of *b*-racemate of α-phenyl-α-piperidyl-(2)-acetic acid are obtained.

EXAMPLE 6.

11 parts by weight of the laevo-rotary *a*-isomer of α-phenyl-α-piperidyl-(2)-acetamide —hereinbefore called a_1-antipode—having a specific rotation $[\alpha]_D^{22} = -68°$ (as 1 per cent solution in 60 per cent ethanol), are refluxed for 6 hours with 12 parts of potassium hydroxide, dissolved in 12 parts by volume of water. After cooling, 10.5 parts by weight of a mixture of a_1-antipode and b_1-antipode of the α-phenyl-α-piperidyl-(2)-acetamide precipitate. The precipitate is suction-filtered, washed with a small amount of cold water, and dried for half an hour at 70° C. under reduced pressure. The material then has a specific rotation $[\alpha]_D^{22} = +41°$ (as 1 per cent solution in 60 per cent ethanol). By recrystallization from 350 parts by volume of ethyl acetate there is obtained a first main fraction of 4.9 parts by weight of b_1-antipode having a specific rotation $[\alpha]_D^{22} = +65°$ (as 1 per cent solution in 60 per cent ethanol). By systematic fractional crystallization it is possible to regenerate from the mother liquors further quantities of b_1-antipode, in addition to 2.5 parts by weight of the originally used a_1-antipode. Yet it is preferable to subject the combined mother liquor products of the first b_1-antipode crystallization to a further alkaline treatment, whereupon a main fraction of pure b_1-antipode can be separated, again by a single crystallization operation from ethyl acetate. This procedure is repeated until practically the entire quantity of a_1-antipode

is converted into the b_1-antipode of the α-phenyl-α-piperidyl-(2)-acetamide.

From 4.5 parts by weight of this b_1-antipode of the α-phenyl-α-piperidyl-(2)-acetamide there are obtained by refluxing for 6 hours with 14.5 parts by volume of 6N-hydrochloric acid and subsequent recrystallization at 20° C. 5.0 parts by weight of the b_1-antipode of α-phenyl-α-piperidyl - (2)-acetic acid hydrochloride having a specific rotation $[\alpha]_D^{22} = +63°$ (as 1 per cent solution in water).

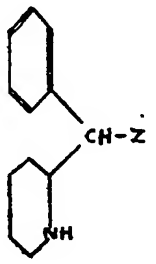
4.5 parts by weight of this substance are dissolved in 12 parts by volume of methanol and refluxed for 2 hours while introducing dry hydrogen chloride gas. On cooling, 3.8 parts by weight of the b_1-antipode of α-phenyl-α-piperidyl-(2)-acetic acid-methyl ester-hydrochloride having a specific rotation $[\alpha]_D^{22} = +89°$ (as 1 per cent solution in methanol) are obtained.

The a_1-antipode of α-phenyl-α-piperidyl-(2)-acetamide used as starting material is obtained in the following manner:

109 parts by weight of *a*-racemate of α-phenyl-α-piperidyl-(2)-acetamide are dissolved in 2500 parts by volume of 96 per cent ethanol and the boiling solution mixed with a boiling solution of 75 parts by weight of *l*-tartaric acid in 2500 parts by volume of 96 per cent ethanol. The mixture is allowed to stand at 20° C. for 15 hours during which 112 parts by weight of the acid α-phenyl-α-piperidyl-(2)-acetamide tartrate crystallize; this salt contains the a_1-antipode in enriched form owing to its higher speed of crystallization. The acid tartrate is dissolved in 500 parts by volume of water, the amide is precipitated with 1.1 equivalents of 10N-caustic soda solution; the preparation and crystallization of the salt by the same procedure is repeated twice with correspondingly smaller amounts of *l*-tartaric acid and solvent. The crude a_1-antipode is crystallized from ethyl acetate to obtain 35 parts by weight of the pure a_1-antipode of α-phenyl-α-piperidyl-(2)-acetamide used for the rearrangement reaction.

What we claim is:

1. A process for the manufacture of the *b*-racemate or *b*-antipode of a compound of the formula



wherein Z represents a free or functionally converted carboxyl group, which consists in treating with an alkaline reagent an *a*-racemate or *a*-antipode of a compound of the above formula.

2. A process according to claim 1, wherein Z represents an ester group.

3. A process according to claims 1 and 2, wherein Z represents a methyl ester group.

4. A process according to claim 1, wherein Z represents the group —$CONH_2$.

5. Process according to claims 1—4, wherein in a resulting *b*-racemate or *b*-antipode of the above formula, wherein Z represents a functionally converted carboxyl group, the functionally converted carboxyl group is converted into a free carboxyl group by methods known per se.

6. Process according to claims 1 to 5, wherein the *b*-racemate or *b*-antipode of α-phenyl-α-piperidyl-(2)-acetic acid is isolated by crystallisation from water.

7. Process according to claim 1—6 wherein the *a*-racemate or *a*-antipode of α-phenyl-α-piperidyl-(2)-acetic acid amide is treated with an alkaline reagent, the *b*-racemate thus obtained is converted into the free acid by treatment with a strong acid, the pure *b*-racemate of α-phenyl-α-piperidyl-(2)-acetic acid is isolated by crystallisation from water at a pH value of about 6 and the free acid is converted into the methyl ester by conventional methods.

8. A process as claimed in any one of claims 1—4 and 7, wherein a pure *a*-racemate or a pure a_1-antipode is used as starting material.

9. A process as claimed in any one of claims 1—4 and 7, wherein a mixture of racemates is used as starting materials.

10. A process as claimed in any one of claims 1—4 and 7, wherein an alkali metal hydroxide is used as alkaline agent.

11. A process as claimed in any one of claims 1—4 and 7, wherein the reaction is carried out at a raised temperature.

12. A process for the manufacture of *b*-racemates or *b*-antipodes of a compound of the formula shown in claim 1 conducted substantially as described in any one of the Examples herein.

13. *b*-Racemates, free from *a*-racemates of a compound of the formula shown in claim 1 and *b*-antipodes of said compounds.

14. *b*-Racemates, free from *a*-racemates, of esters of α-phenyl-α-piperidyl-(2)-acetic acid, and b_1-antipodes of the said compound.

15. The *b*-racemate, free from *a*-racemate, of α-phenyl-α-piperidyl-(2)-acetic acid methyl ester.

16. *b*-Racemates, free from *a*-racemates, of amides of α-phenyl-α-piperidyl-(2)-acetic acid, and b_1-antipodes of the said compounds.

17. The *b*-racemate of α - phenyl - α-piperidyl-(2)-acetic acid amide free from *a*-racemate.

18. The *b*-racemate of α - phenyl - α-piperidyl-(2)-acetic acid free from *a*-racemate.

19. The b_1-antipode of α - phenyl - α-piperidyl-(2)-acetic acid methyl ester.

20. The b_1-antipode of α - phenyl - α-piperidyl-(2)-acetic acid amide.

21. The b_1-antipode of α - phenyl - α-piperidyl-(2)-acetic acid.

22. The *b*-racemates, free from *a*-racemates, and the *b*-antipodes of the compounds of the formula shown in claim 1 as described in the Examples.

23. A pharmaceutical preparation containing, together with a carrier substance, a *b*-racemate, free from *a*-racemate, or a *b*-antipode of an α-phenyl-α-piperidyl-(2)-acetic acid ester.

24. A pharmaceutical preparation containing, together with a carrier substance, the *b*-racemate of α - phenyl-α-piperidyl-(2)-acetic acid methyl ester free from *a*-racemate.

25. A pharmaceutical preparation containing, together with a carrier substance, the b_1-antipode of α-phenyl-α-piperidyl - (2)-acetic acid methyl ester.

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